An Interactive Technique for Optimizing Drug Development fr m the Pre-clinical Phases through Phase-IV

I. DESCRIPTION

I.A. Related Applications

[01] This Application claims priority from co-pending U.S. Provisional Application Serial No. 60/410,803 filed September 16, 2002, the contents of which are incorporated herein by reference. The disclosure of U.S. Application 09/691,053, filed October 19, 2000, is also incorporated herein by reference.

I.B. Field

[02] The disclosed teachings relate to an interactive technique for performing the testing of a new drug and its development from phase I - phase IV testing.

I.C. Background

1. References

[03] The following papers provide useful background information, for which they are incorporated herein by reference in their entirety, and are selectively referred to in the remainder of this disclosure by their accompanying reference keyword in square brackets (i.e., 3. for the reference by Dodion et al.)

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2. Introduction

[04] The drug industry is facing substantial challenges with regards to cost-containment and time-to-market for its high-potential candidates. Currently pharmaceutical companies investigate many different methods for increasing their productivity in the development process in order to compensate for increasing difficulties in recouping the investment in drug development.

[05] However, the classical method of clinical trials design [1,2] suffers major drawbacks. On the one hand, developing drugs by "trial and error" alone can not guarantee that the selected schedules are better than other, yet to be tried,

treatment regimens. On the other hand, the number of schedules which can be empirically tested is negligibly small with respect to the potential number of sensible schedules.

[06] Research shows that the effects of the drug may crucially correlate with the internal dynamics of the tumor growth processes, as well as with the relevant patient's physiology. These aspects might often be too complex to be estimated by the naked eye, and slight nuances in the treatment schedule may be critical for the effect achieved [8-11]. In theory, if all potential treatment schedules could be tested, considering all the available information on the involved biological processes, pathological processes and the momentary effect of the drug on every element of these processes, one could, a-priori, suggest a theoretical set of the most promising treatment schedules for a given indication, or, even, for a given patient. Subsequently, these promising schedules would be clinically tested, thus saving human resources and time, and helping to achieve maximal possible therapeutic effects of the tested drug.

[07] Needless to say that such methods would enable to rehabilitate drugs with valid properties, which failed during the development process, due to insufficient efficacy, or limitations of toxicity, which could possibly be overcome by modifying the treatment schedule. In addition, these methods would enable a "Go–NoGo" decision to be made early during the clinical trial process.

3. Definitions and notations

[08] For ease of understanding of the present specification, the following abbreviations/ notations are used:

A_1-A_3 - constants

B_1-B_3 - constants

BL - blood

c - elevation increment of drug concentration

C_{Di} - the concentration after administrating the given dose in blood

C_{Dij} - the concentration after administering the given dose "i" in target tissue "j"

C_{Dik} - the concentration after administering the given dose "i" in toxicity tissue "k"

C_I - drug concentration

CmC - a control group for combinational therapy (patients treated by today's first line therapy)

CT - clinical trial

d – elevation increment of the drug dose

D_0(PhI) - initial dose proposed for Phase I clinical trial

D_i-dose administered

DLT – dose-limiting toxicity

D_n - dose for a given variant of the protocol proposed by the model for testing

D_o-D_f - initial dose to final dose,

EC - effective concentration

E_{ci} - effect of the drug at the given concentration

E_{cij} - effect of the drug at the given concentration "i" on target tissue "j"

E_{Cdik} - effect of the drug at the administered dose "i" on toxicity tissue "k"

EC_n - effective concentration n, the concentration giving n percent of maximal effect

ED - effective dose

E_{Dij} - the efficacy after administering the given dose "i" in target tissue "j"

F1, F2, F3 – counters

G_O-a rationale to continue developing the drug

Group Ci - group of patients for combinational treatment by protocol I (CTPi) for indication cancer type I (CTi)

Group Mi - group of patients for monotherapy treatment by protocol I (MTPi) for indication cancer type I (CTi)

h-of human tissue/cell culture

h_{tc} - human tumor cells

K1, K2-counters

LD_n - lethal dose n, i.e. a dose causing n percent of death in the tested animals group

MA, MB, MC – number of tests in which the drug effect remains < X, when escalating concentrations, for stopping further dose escalation

MED - Minimum Effective Dose, a dose at which the effect was first observed

MnC - a standard monotherapy treatment group (patients treated by today's first line therapy)

MTD – maximal tolerated dose (after which the DLT is observed)

n_1 – number of steps to be defined in order to going from mED to MTD;

n_2 - number of steps to be defined to go from mED to RD

nr - nonrodent species

NO GO – no rationale to continue developing the drug.

P - percent of animals that died

PD - pharmacodynamics

PK - pharmacokinetics

r - of rodent tissue/cell culture

r/h_{Tox} - rodent or human toxicity

r_{tc} - rodent tumor cells

RD - recommended dose

s_1-s_2 - constants

T_n - dose interval for a given variant of the protocol proposed by the model for testing

Tox - the tissue in which a toxic effect occurs ("toxicity" tissue)

TT - target tissue

VPE - Virtual Patient Engine

X – accepted threshold ("asymptote") of differences in the effect after elevation of concentration by one increment (c).

Z1, Z2, Z3 -counters

II. SUMMARY

[09] To realize advantages noted above, there is provided a method of performing interactive clinical trials for testing a new drug comprising performing a pre-clinical phase in which a computer model for pharmacokinetics and pharmacodynamics of the drug is created and adjusted based on in vitro studies and in vivo studies in animals. A phase I clinical research is performed in which a clinical trial on at least a single dose is performed in parallel with performing computer simulation studies

using the computer model. The computer model is adjusted based on comparison of the results of the clinical research and the computer simulation. A maximal tolerated dose, minimum effective dose, and a recommended dose is determined based on the phase I clinical research in conjunction with the computer simulations. The drug is checked for cumulative effects and providing this information to the computer model. Multiple simulations are performed using the computer model with different doses and dosing intervals. An optimal protocol is determined for the most responsive patient populations and indications for a phase II clinical trial. Phase II clinical trial is performed where a number of small scale clinical trials are performed in parallel based on results of the above. The interim results are analyzed to choose the most promising regimens for continued clinical trials. Phase III clinical research is performed for chosen indications by chosen protocols. Phase IV studies are performed for post-marketing subpopulation analysis and long term product safety assessment.

[10] In a specific enhancement during phase I studies, prior to each sub-step of the phase I trial, computer simulation is performed to predict results of the sub-step and the predicted results are compared to clinical results corresponding to the sub-step and the computer model is adjusted based on the comparison.

[11] In another specific enhancement, a first decision whether to continue with the trial is made, stopping the trial if an adverse decision is made.

[12] In another specific enhancement, the results of determination of the optimal protocolare used to define indications and define sub-groups of patients most sensitive, susceptible and responsive to the drug.

[13] More specifically, effective treatment protocol is defined for a subset of the subgroups.

[14] In yet another specific enhancement the computer model is adjusted based on whether the clinical research indicates a result higher than a threshold in at least one of pre-clinical, phase I and phase II studies.

[15] In still another specific enhancement during phase II trial, small clinical trials are performed in parallel for a chosen indication by a chosen treatment protocol.

[16] In still another specific enhancement, in analyzing interim results, the most promising trials are chosen for indications most sensitive to the drug administered via the most efficient protocol.

[17] More specifically, in analyzing interim results, a second decision whether to continue with the trial is made, stopping the trial if an adverse decision is made.

[18] Even more specifically the second decision is based on a prediction of safety profile of the new drug in the most promising trial compared with safety of pre-existing therapies.

[19] Still more specifically, the second decision is based on a prediction of efficacy profile of the new drug in the most promising trial compared with efficacy of pre-existing therapies.

[20] In yet another specific enhancement, phase III clinical research is performed to prove safety of the drug.

[21] In yet another specific enhancement, phase IV clinical research is performed to prove efficacy of the drug.

[22] In still another specific enhancement, when hitherto unknown effects are discovered, the computer model is adjusted to obtain predictions for new protocols, patient populations and indications.

[23] Another aspect of the disclosed teachings is a method of performing interactive clinical trials for a new drug comprising a step of performing a pre-clinical phase in which a computer model for pharmacokinetics and pharmacodynamics is created and adjusted based on in vitro studies and in vivo studies in animals.

[24] Still another aspect of the disclosed teachings is a method of performing interactive clinical trial for a new drug comprising a step of performing a phase I clinical trial wherein a dose-escalation trial is performed in parallel with computer simulation studies to predict results and the prediction is compared with clinical results and the comparing is used to adjust the computer model.

[25] Still another aspect of the disclosed teachings is a method of performing interactive clinical trials for a new drug comprising developing a strategy for a next sub-step in phase I clinical trial in conjunction with simulated computer predictions.

III. BRIEF DESCRIPTION OF THE DRAWINGS

[26] The disclosed teachings will become more apparent by describing in detail examples and embodiments thereof with reference to the attached drawings in which:

[27] Fig. 1 shows duration and number of patients (averages) to be engaged in the Interactive Clinical Trial Design as compared to those in the classical design

[28] Fig. 2A A classical clinical trial protocol for drug "O" as compared to an example implementation of the disclosed interactive clinical design protocol based on stages of implementing an example implementation of the disclosed teachings.

[29] Fig. 2B-E various stages of an example implementation.

[30] Fig. 3 shows an example of adaptive trial design as compared to the classical design.

[31] Fig. 4 shows an overall diagram of an example implementation of the disclosed interactive clinical trial technique

[32] Fig. 5A shows a panel of an example implementation of the disclosed interactive trial design in the preclinical research stage

[33] Fig. 5B shows a panel of an example implementation of the disclosed interactive trial design in the preclinical research stage (con't)

[34] Fig. 5C shows one panel of an example implementation of the disclosed interactive trial design in the preclinical research stage (con't)

[35] Fig,. 5D shows a summary of the preclinical research stage

[36] Fig. 5E shows one panel of an example implementation of the disclosed interactive trial design in the Phase I trial stage

[37] Fig. 5F shows one panel of an example implementation of the disclosed interactive trial design in the Phase I trial stage (con't)

[38] Fig. 5G shows one panel of an example implementation of the disclosed interactive trial design in the Phase I trial stage (con't)

[39] Fig. 5H shows one panel of an example implementation of the disclosed interactive trial design in the Phase I trial stage (con't)

[40] Fig. 5I shows an example of a computer simulation between Phase I and Phase II.

[41] Fig. 5J shows one panel of an example implementation of the disclosed interactive trial design in the Phase II trial stage.

[42] Fig. 5K shows one panel of an example implementation of the disclosed interactive trial design in the Phase II trial stage (con't)

[43] Fig. 5L shows one panel of an example implementation of the disclosed interactive trial design in the Phase III trial stage.

[44] Fig. 5M shows one panel of an example implementation of the disclosed interactive trial design in the Phase IV trial stage.

[45] Fig. 6 shows an example of an overall framework for treatment optimization.

IV. DETAILED DESCRIPTION

IV.A. Synopsis

[46] Today, there exist elaborate and highly interdisciplinary and multidisciplinary methods, which can employ modern computing facilities for integrating the enormous body of relevant biological, medical, pharmacological and mathematical (dynamical) information into comprehensive systems for simulating different drug treatment scenarios. The techniques disclosed herein are based on more than two decades of biomathematical research in the area of disease control optimization [8-28]. Thus, mathematical algorithms have been developed, which simulate the dynamics of key biological, pathological and pharmacological processes in a patient undergoing drug treatment, either by monotherapy, or by combination of cytotoxic and/or cytostatic agents, and/or by growth-factors. This set of computerized mathematical models, in conjunction with advanced optimization algorithms have

now yielded an in silico patient engine, having a range of applications designed to deliver optimal drug treatments for cancer and hematological disorders [eg., 28-29].

[47] Disclosed herein are techniques for improving anticancer drug development, which employ such an in silico patient engine in drug development. The disclosed techniques enable the drug developer an ongoing dialogue, from pre-clinical phase through Phase-IV, for generating, fine-tuning and validating a reliable drug/disease/host model. Thus, relatively early during development, i.e., by the end of Phase-I, and no later than in mid-Phase-II, the model already contains the precise PK/PD drug parameters, to be implemented in the in silico patient simulations. At this stage numerous drug schedules (termed "infinite protocol space") are simulated for any desired indication, and proprietary optimization techniques are employed for selecting, among the vast number of simulation scenarios, those yielding best results according to the list of specifications set by the drug developer. In this way one identifies the most appropriate indications/monotherapy/combination treatments for the drug. At this early stage a "Go -NoGo" decision can be made.

[48] Following the disclosed techniques clinical trials can be rationally designed, which will be based upon a gradual improvement and zeroing-in on the best prediction-directed treatment schedules. It is important to stress that the disclosed technique carries little risk of yielding false predictions, since the algorithm has been designed so as to be continuously validated and improved by information derived in parallel from clinical trials.

[49] An overall framework for treatment optimization is shown in Fig.6. In the In Silico Patient modules mathematical algorithms for disease process, physiological processes & drug PK/PD are computerized. In the treatment Optimization Module – optimal treatments satisfying user's (eg., Pharma) specifications are predicted.

Illustrative example

[50] Fig. 4 shows an example implementation of the disclosed techniques. It should be noted that the scope of the disclosed technique is not limited specifically to this example implementation which is merely illustrative and exemplary in nature.

1. Pre-Clinical Phase: Constructing the PK/PD Module

[51] The pre-clinical phase of drug development is dedicated to retrieval of the drug's pharmacodynamics (PD) and pharmacokinetics (PK) in animals and to initializing human PD research. In this phase the computer model is adjusted to the drug under development, as is detailed below.

[52] Based on the in vitro studies the drug PD module is constructed. Putative mechanisms of drug action are simulated, retrieving the most appropriate mechanism in the animal trials. From the results of the in vitro studies, the parameters of drug's effect on the different target tissues are empirically estimated and inputted into the module. These include the data of experiments using different tumor types, possibly in combination with another drug. Inversely, the model here can simulate and comparatively estimate the efficacy of the treatment in combination with other known drugs, as well as the effect of the drug on different

tumor types. In this way the pre-clinical research can be directed to the most effective avenues. The model is continuously fine-tuned, by "on-line" implementation in the In Silico Patient, of the pre-clinical research results. Thus, the model interactively guides the empirical research to reveal the further necessary data.

[53] Using animal studies, the PK module is adjusted to describe the PK of the given drug,. The PD module, which until now was based on the in vitro data only, is adjusted to represent the in vivo results, and is supplemented with animal parameters for the functions of drug effect time series. This, again, includes data on different tumor types and on the effects of combinations with other drugs. From animals treated by multiple doses, some data on cumulative effect can be obtained and implemented in the model.

[54] The toxicity module is designed to include the qualitative and quantitative data on the side effects observed during the animal studies. In this way the module describing hemopoietic processes is provided with parameters of the drug effect on hemopoiesis, if observed in animals; other toxicities observed are described as a function of the drug time course. From animals treated by multiple doses, some data on cumulative toxicity may be obtained and implemented in the model as well.

[55] At this stage the model already has the capacity to make approximate predictions on the administration of the drug to humans. Known inter-species differences in the effected tissue characteristics are taken into account when simulating the human PK model, in order to consider a reasonable dose range for Phase-I human studies. That procedure is expected to offer an improvement of the traditional LD10/10 initial dose for Phase-I trials, which is often too low to have any

effect on the disease. That is to say that already in this stage, based on in vitro and in vivo data the model can be used for predicting the minimal dose within therapeutic range, i.e. the lowest dose, which has a rationale to be tested. It is possible at this point to use the model for predicting failure of the drugs with therapeutic doses too toxic to be tolerated.

[56] Fig. 5A shows an example implementation of the phase of pre-clinical research where the pharma company checks the in vitro effect of the drug concentrations in human cells and in rodent cells. The idea is to escalate the dose until there is no additional effect.

[57] Fig. 5B shows an example implementation of the phase of pre-clinical research where the pharma company checks the in vivo effect of the drug concentrations in rodents. The idea is to calculate the LD10(r) in rodents. Since the work in done in vivo, if animal death is observed, then at least the reason for the lethal effect can be partially clarified by calculating the effect of the drug administered at dose " i" in rodent or human toxicity tissue "k", i.e. ECDik(r/htox).

[58] Fig. 5C shows an example implementation of the phase of pre-clinical research where the pharma company checks the in vivo effect of the drug concentrations in a nonrodent species. This is necessary in order to determine the initial dose of the drug (D0(PhI)) to begin Phase I clinical studies. The LD(nr) is calculated and compared to the LD10(r) and with this information D0(PhI) can be calculated.

[59] Fig. 5D shows a summary table of all the data used to develop the PK/PD model. The shaded boxes in the table stand for concrete numbers.

2. Phase-I: Finalizing and Validating the PK/PD Module

[60] During dose escalation testing in the Phase-I trials, the computer model (in silico patient) interacts with the trial, predicting the results for every step in the trial and, at termination of every step, is updated by implementing the observed effect and toxicity. In this way the computer model (in silico patient) is continuously validated and fine-tuned, to give better predictions in the next step. This could, possibly, save steps during dose escalation, which is necessary for obtaining the toxicity profile and an initial efficacy profile. During Phase-I trials, while using the intra-patient dose escalation method, the model is provided with data on cumulative effect and cumulative toxicity, if observed.

[61] In this way, by the end of Phase-I, a fully verified in vivo human model is available, integrating all the existing data on PK and PD of the drug.

[62] Fig. 5E shows an example implementation of steps in Phase I clinical research where the pharma company performs the clinical trial in parallel to computer simulations. The on-line cooperation between pharma's clinical trial and simulations can greatly facilitate the determination of the minimal effective dose (mED). If it is seen in simulation that mED > MTD (maximum tolerated dose), then an early NOGO decision can be made. At the same time, an early calculation of the dose elevation increment of the drug, d, can be made. In addition, in this stage, if the simulation results show that the clinical trial (CT) results > a chosen threshold (X), then the PK/PD model can be adjusted.

[63] Fig. 5F shows an example implementation of steps in Phase I clinical research where the pharma company performs the clinical trial on the drug in parallel to computer simulations based on the disclosed techniques. Here, the MTD is determined and again, at this point, the algorithm allows an early determination

of the dose escalation step, d. In addition, in this stage, if the simulation results show that the clinical trial (CT) results > a chosen threshold (X), then the PK/PD model can be adjusted.

[64] Fig. 5G shows an example implementation of steps in Phase I clinical research where the pharma company performs the clinical trial on the drug in parallel to computer simulations based on the disclosed techniques. Here, the algorithm allows an early determination of the recommended dose (RD). Here again, the dose escalation step (d) is calculated. In addition, in this stage, if the simulation results show that the clinical trial (CT) results > a chosen threshold (X), then the PK/PD model can be adjusted.

[65] At this point, the PK/PD model is completed. Also, MTD, mED and RD have already been calculated. Now, as shown in Fig. 5H many simulations are performed with different doses and dosing intervals. With these parallel virtual trials, the drug's cumulative effect is checked and again, if the simulation results show that the clinical trial (CT) results > a chosen threshold (X), then the PK/PD model can be adjusted as necessary.

3. Interim Stage Between Phase-I and Phase-II: Intensive Simulations of Short-Term Treatments

[66] Following Phase-I the model can yield reasonable, short-term predictions concerning the effects of definite drug administration schedules on disease progression for specific indications. This allows one to perform an exhaustive search in the protocol space (i.e., within all the treatment schedule possibilities), for those mono- and combination therapy schedules, which are expected to yield the highest response and lowest toxicity for any potential cancer type to be treated. This may help the drug developer to predict the most effective treatment schedule and the

most promising indication, thus saving patient health, and time and costs of the drug's development.

[67] Fig. 5I shows example implementations of steps in between Phase I and Phase II. At this point, many simulations are carried out with different cancer types in order to find the optimal protocol for different patient populations and different indications. The optimized result can then be compared with the first line therapy. At the end of this step, one can recommend which indications and patient populations to continue with to Phase III. Lastly, a GO-NoGo decision can be made at this point.

4. Phase-II and Phase-III: Focusing the Clinical Trials

[68] At the onset of Phase-II trials and following the interim stage outlined in section 3, a few proposed treatment schedules for the selected indication(s) are applied in short pilot trials testing a relatively small number of patients. After the first results are obtained (supposedly 6 months on average), the model should be adjusted by implementing the new data on the observed effects (including that indicated by surrogate markers).

[69] Subsequently, a new set of intensive simulations is carried out, predicting disease progression during an extended period of up to two years , and predicting which of the schedules, tested in short-term trials, are expected to yield the best results in the long-run (changes can be made to the schedules in accordance with the model predictions). At this stage the predicted effect for each selected schedule is compared with that of existing therapies for the same indications. The model allows personalization for the patients involved in the study, based on the results obtained after the first 6 months, to yield more precise predictions.

[70] At this stage, the model can predict failure, that is, recommend a NoGo decision, for the drugs that are incapable of demonstrating benefit over the existing therapies. The schedule(s) predicted to carry the most significant benefit over the existing treatments are selected for further testing in Phase-III. After the efficacy and safety profile of the selected schedule(s) is confirmed in further Phase-II trials (for another 6 months), the selected schedules should be further tested in extended group of patients as Phase-III trials.

[71] Fig. 5J shows an example implementation of steps of Phase II clinical research where the pharma company performs a series of small clinical trials in parallel with small numbers of patients. Recommendations from the model are tested in these trials. From this group of clinical trials, the interim results at 6 months are analyzed and long term computer simulations (simulated for a period of 2 years) are performed. From all of these small parallel clinical trials, the most promising are chosen to continue for another 6 months in parallel.

[72] As shown in Fig. 5K Phase II is continued with the most promising trials in parallel for another 6 months. Again, there is another round of data analysis, long term simulations and finally, the optimal protocol is chosen to continue to Phase III studies.

[73] Further, as shown in Fig. 5L Phase III studies are carried out in a large number of patients and compare the test drug to standard therapy. The disclosed techniques thereby streamline the clinical development process by combining Phase II and III and efficiently contribute to an expedited FDA submission.

[74] Finally, as shown in Fig. 5M, Phase IV studies are carried out after market approval and long term safety assessment and subpopulation analyses are carried

out in the virtual patient engine (VPE). If rare side effects or unexpected drug interactions are found in certain subpopulations, then the disclosed technique can recommend to which step the developer should go back to in order to improve drug performance

[75] The example implementation of the interactive clinical trial design was compared to a classical clinical trial design of anti-cancer drugs (denoted original). Fig. 1 illustrates the average differences in the number of patients expected to be engaged in the clinical trials designed according to each of the two methods.

[76] One can notice in this figure a significant predicted saving in time and in the number of patients, which the technique of interactive clinical trials design offers. Figs 2A-2E schematically present the results of the theoretical comparison between the classical design in the development of a test drug "O", currently in Phase II-III in one of the big Pharma companies and the design of the same drug under the interactive clinical trials technique; the differences (in percentage) in the number of patients and the total duration of drug development are noted at the bottom of Figs. 2B-2E.

IV.B. Interactive Clinical Trial Design as compared to the Adaptive Trial Design method

[77] "Adaptive designs are dynamic". They are based on the assumptions of Bayesian statistics (in contrast to the classical design, which is based on frequentists assumptions). Adaptive design trials suggest an improvement to the classical design, as they offer ability to stop trials relatively early, drop or add treatment groups, change group proportions or shift seamlessly into a later phase, etc. These models aid in planning trials by predicting the probability distribution of trial outcomes conditional on current knowledge and assumption, and thus

evaluating the ability of the trial to support a certain decision. These models rely upon prior probability distribution (e.g. Fig. 3) [30-33].

[78] By comparing Figure 3 to Figure 1, one can immediately notice the main differences between the two methods: (a) the point of influence of the Interactive Design can be as early as the Pre-clinical stage, whereas to the point of influence of the Adaptive Design begins only in Phase-II; (b) moreover, while the first and potentially most important decision-making impact of the Interactive Trial Design takes effect already at the end of Phase-I, the Adaptive Trial design's impact can be effectuated only towards the end of Phase-III. The reason for these differences lies in the significant distinction between the tools employed by each of the designs. A major asset offered by the disclosed technique is its predictive power, rather than the improved data analysis methods, offered by the Adaptive Design. In other words, the disclosed design is primarily prospective, integrating all the available biological, medical, pharmacological, theoretical and clinical information. In contrast, Adaptive design is primarily retrospective, integrating statistical methods with the information from the clinical trials

[79] Other modifications and variations to the invention will be apparent to those skilled in the art from the foregoing disclosure and teachings. Thus, while only certain embodiments of the invention have been specifically described herein, it will be apparent that numerous modifications may be made thereto without departing from the spirit and scope of the invention.